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INTELLECTUAL PROPERTY OFFICE OF THE PHILIPPINES

To All To Whom These Presents Shall Come:

This is to Certify that the annexed is a true copy from the records of this Office of the original, consisting of the Request for Grant of a Philippine Patent Specification & Claims; Abstract and Drawings (if there is any), and other relevant documents as originally filed in:

Pending Patent Application of

TAN, MA. TERESA Y.
9-E Lantana St., Quezon City
Philippines 1112

SINGH, EULOGIO
7 Sampaguita Drive, Aranzazu
Subdivision, Rizal
Phlippines 1860

SANTOS, RITA JOSEFINA M.
5 Andres Malong, Project 4
Project 4, Quezon City
Philippines

DEE, KENNIE U.
59D, 12th Street, corner Gilmore Ave.
New Manila, Quezon City
Philippines

Appl. No. : **1-2003-000285** Filed: **June 6, 2003**

Inventor(s): **Tan, Ma. Teresa Y., et al.**

for

Invention: **PHARMACEUTICAL COMPOSITIONS**

In witness whereof, I have hereunto affixed my hand and the seal of the Intellectual Property Office at Makati City, Philippines, this **24th day of January, 2006**

EPIFANIO M. EVASCO
Director
Bureau of Patents

Attested:

EVELYN M. MAN[illegible]C
BOP, Records Officer III

Doc. No.: BOP-014
Series of: 2006
Requested by: **Ma. Joyce B. Santos**

CERTIFIED COPY OF PRIORITY DOCUMENT

REQUEST FOR GRANT OF A PHILIPPINE PATENT

(The following is to be filled in by the Intellectual Property Office)
APPLICATION No.: 1-2003-000285
FILING DATE:
Date of Receipt: 06 June 2003

THE UNDERSIGNED HEREBY REQUEST GRANT OF A PHILLIPINE PATENT FOR THE SUBJECT APPLICATION.

Box No. 1 TITLE OF THE INVENTION
PHARMACEUTICAL COMPOSITIONS

Box No. II APPLICANT (WHETHER OR NOT ALSO INVENTOR). Use this box for indicating the applicant or, if there are several applicants, one of them. If more than one person (include, where applicable, a legal entity) is involved, continue in supplemental box.

INTELLECTUAL PROPERTY OFFICE PAID DATE JUN 06 2003 AMOUNT OR NUMBER 1,000.00 10127-20

The person in this box is (check one only): ☒ applicant and inventor ☐ applicant only

Name and address:
Tan, Ma. Teresa Y.
9-E Lantana St.
Quezon City
Philippines 1112

Telephone number: (632) 631-8501 Loc 8460 Fax Number: (632) 635-7464 E-mail address: mytan@unilab.com.ph
(including area code)

Country of Nationality: Philippines Country of residence: Philippines

Box No. III INVENTOR/S. A separate sub-box has to be filled in respect of each person. If the following two sub-boxes are insufficient, continue in the "Supplemental Box". (giving therein for each additional person the same indications as those requested in the following two sub-boxes) or by using a "continuation sheet."

The person in this box is (check one only): ☒ applicant and inventor ☐ inventor only

Name and address:
Singh, Eulogio
7 Sampaguita Drive
Aranzazu Subdivision
Rizal
Philippines 1860

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:
Country of nationality: Philippines Country of residence: Philippines

'03 JUN -6 P3:05

The person in this sub-box is (check one only): ☒ applicant and inventor ☐ inventor only

Name and address:
Santos, Rita Josefina M.
5 Andres Malong
Project 4
Quezon City
Philippines

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:
Country of nationality: Philippines Country of residence: Philippines

IPO-BP Form1A

Box No. IV AGENT(IF ANY) OR COMMON REPRESENTATIVE(IF ANY); ADDRESS FOR NOTIFICATIONS (IN CERTAIN CASES) A common representative may be appointed only if there are several applicants and if no agent is or has been appointed: The common representative must be one of the applicants. The following person (include, where applicable, a legal entity) is hereby/has been appointed as agent or common representative to act on behalf of the applicant(s) before the Intellectual Property Office.

Name and address, including postal codes:
Santos, Ma. Joyce Bedelia B.
637-A San Rafael St
Mandaluyong City
Philippines 1550
Telephone number: (632) 631-8501 Loc 8458 Fax No.: (632) 635-7464 E-mail address: jsantos@unilab.com.ph
(including area code)

Box No. V PRIORITY CLAIM (IF ANY). The priority of the following earlier application(s) is hereby claimed:

Country in which it was filed:	Filing date (month, day, year)	Application No.
(1)		
(2)		
(3)		

Box No. VI SIGNATURE OF APPLICANT(S) OR AGENT OVER PRINTED NAME(S)

Ma. Teresa Y. Tan

Eulogio Singh

Rita Josefina M. Santos

Kennie U. Dee

Box No. VII CHECKLIST (To be filled in by the applicant)

This application contains the following number of sheets:

1.	request	3	sheets
2.	description	7	sheets
3.	claims	2	sheets
4.	abstract	1	sheets
5.	drawing(s)	____	sheets
	Total	**13**	**sheets**

Figure number _____ of the drawing (if any) is suggested to accompany the abstract for publication

This application as filed is accompanied by the items checked below:

- ☐ separate notarized power of attorney
- ☐ copy of general power of attorney
- ☐ priority document(s) (see Box No. V)
- ☐ cheques for the payment of fees
- ☐ other document(specify

IPO-BP Form 1B

Continuation of Box No. III

Supplemental Box. Use this box in the following cases:

i. if more than three persons are involved as applicants and/or inventors: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;
ii. if there are more than three earlier applications whose priority is claimed; in such case, indicate "continuation of Box No. V" and indicate for each additional earlier application the same type of information as required in Box No. V.
iii. if, in any of the Boxes, the space is insufficient to furnish the information; in such case, write "continuation of Box No..." (indicate the number of the box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient.

The person in this sub-box is (check one only): ☒ applicant and inventor ☐ inventor only

Name and address:
Dee, Kennie U.
59D, 12th Street, corner Gilmore Avenue
New Manila
Quezon City
Philippines

If the person identified in this sub-box is applicant (or applicant and inventor), indicate also:
Country of nationality: Philippines Country of residence: Philippines

If this supplemental Box is not used, this sheet need not be included in the Request.

IPO-BP Form 1C

PHARMACEUTICAL COMPOSITIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a solid oral dosage composition of cefuroxime axetil comprising a tablet inside a capsule, the capsule serving to mask the bitter taste of the drug upon oral administration. It has been found that this tablet-in-a-capsule format is bioequivalent to the commercial film-coated tablet.

Description of Related Art

Cefuroxime, as disclosed in US patent 3,974,153, is a broad spectrum second-generation cephalosporin characterized by high activity against a wide range of gram-positive and gram-negative bacteria, this property being enhanced by the very high stability of the compound to ß–lactamases produced by a range of gram-negative microorganisms. Cefuroxime and its salts are used as injectable antibiotics since they are poorly absorbed from the gastro-intestinal tract.

Esterification of the carbonyl group of cefuroxime as a 1-acetoxyethyl ester to give cefuroxime axetil improves the effectiveness on oral administration as described in US patent 4,562,181. This patent further discloses that it is particularly advantageous to use cefuroxime axetil in its amorphous form to enhance dissolution and hence bioavailability.

Cefuroxime axetil has an extremely bitter taste which is long lasting and which cannot be adequately masked by addition of sweeteners and flavors. The tablet needs to be film-coated to eliminate the bitter taste. However, as described in US patent 4,897,270, the film coating must rupture in less than 40 seconds when measured by a rupture test wherein the tablet is placed in a beaker of still 0.07 N hydrochloric acid at 37° C. When the film coating is too thick, the slow permeation of water through the film coating to the core will cause gel formation of the amorphous cefuroxime axetil core leading to poor dissolution and bioavailability. The rupture time of less than 40

seconds for the film coating prevents gel formation while at the same time providing adequate barrier against the bitter taste of the medicine. Amorphous cefuroxime axetil film-coated tablets are commercially available from Glaxo USA under the brand name Ceftin®.

SUMMARY OF THE INVENTION

The present invention provides a solid oral dosage composition of cefuroxime axetil comprising a tablet inside a capsule, the capsule serving to mask the bitter taste of the drug upon oral administration. It has been found that this tablet-in-a-capsule format is bioequivalent to the commercial film-coated tablet.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises a core tablet of substantially amorphous cefuroxime axetil inside a capsule. The core tablet is preferably shaped like a capsule (caplet).

The core tablet comprises more than 10% w/w of a distintegrant, preferably more than 15% w/w, and most preferably 20% w/w. The disintegrant includes but is not limited to starches, clays, celluloses, algins, gums, cross-linked polymers, and combinations thereof. The preferred disintegrants are microcrystalline cellulose, starch, croscarmellose, crospovidone, sodium starch glycolate, and combinations thereof.

In addition to the active ingredient and disintegrant(s), the core tablet may contain a number of other ingredients referred to as excipients. These excipients include among others diluents, binders, lubricants, glidants, and colorants.

The core tablet is filled into a capsule which is generally a two-piece hard gelatin capsule, but capsules made from hydroxypropylmethylcellulose, vegetable or plant-based cellulose, polysaccharides and other polymers can also be used.

We have surprisingly found that the composition of this instant invention is bioequivalent to the commercial film-coated tablet even if the rupture time of the capsule is in excess of 60 seconds. In contrast, the same amount of formulation filled into capsules without tabletting results in gel formation and consequently poor dissolution. Not wishing to be bound by theory, it is believed that tabletting results in a higher disintegration force that causes the rupture of the capsule by the caplet before gel formation occurs, especially in the central overlap region of the capsule which is twice as thick as ends.

The thickness and width of the caplet is preferably greater or equal to 65% of the internal diameter of the capsule, more preferably greater or equal to 75%, and most preferably greater or equal to 80%.

Example 1

Ingredients	Mg/capsule
Amorphous Cefuroxime Axetil	301.6*
Starch	93.6
Croscarmellose sodium	66.0
Sodium lauryl sulfate	5.0
Colloidal silicon dioxide	1.5
Total weight	467.7

* Equivalent to 250 mg of cefuroxime

Cefuroxime axetil, starch, croscarmellose, sodium lauryl sulfate, and colloidal silicon dioxide were blended together, and compacted into granules with a roller compactor. The granules were filled into size no. 1 two-piece hard gelatin capsule.

Dissolution was carried out according to USP 26 in 900 ml of 0.07 N HCl at 37° C, in USP apparatus II.

Time (min)	Cumulative percent drug released
15	52.4%
45	65.7%

The dissolution fails to comply with the USP requirement for cefuroxime axetil of not less than 65% dissolved in 15 minutes, and not less than 75% in 45 minutes. Gel formation was observed in the central overlap region of the capsule; this gel persisted even after the capsule has dissolved.

Example 2

The granules of Example 1 were compressed into 467.7 mg caplets using a Manesty BB3B tabletting machine. The size of the caplet is 18 mm x 5.7 mm x 5.1 mm (length x width x thickness) with a hardness of 6-10 kp. The caplets were manually filled into size no. 1 two-piece hard gelatin capsules. The dimension of the capsule is 19.4 mm x 6.4 mm (length x internal diameter).

Dissolution was carried out according to USP 26 in 900 ml of 0.07 N HCl at 37° C, in USP apparatus II.

Time (min)	Cumulative percent drug released
15	92.6%
45	98.5%

The dissolution complies with the USP requirement for cefuroxime axetil of not less than 65% dissolved in 15 minutes, and not less than 75% in 45 minutes. Gel formation was not observed. The mean rupture time of the caplet-in-capsule is about three minutes.

Comparison of Example 1 and Example 2 clearly shows suppression of gel formation and thus improved dissolution when the same amount of granules is tabletted before filling into the capsule.

Example 3

Ingredients	Mg/capsule
Amorphous Cefuroxime Axetil	603.2*
Starch	187.1
Croscarmellose sodium	32.1
Sodium lauryl sulfate	10.0
Colloidal silicon dioxide	3.0
Total Weight	835.4

* Equivalent to 500 mg of cefuroxime

Cefuroxime axetil, starch, croscarmellose, sodium lauryl sulfate, and colloidal silicon dioxide were blended together, and compacted into granules with a roller compactor. The granules were filled into size no. 00 two-piece hard gelatin capsule.

Dissolution was carried out according to USP 26 in 900 ml of 0.07 N HCl at 37° C, in USP apparatus II.

Time (min)	Cumulative percent drug released
15	35.4%
45	42.2%

The dissolution fails to comply with the USP requirement for cefuroxime axetil of not less than 65% dissolved in 15 minutes, and not less than 75% in 45 minutes. Gel

formation was observed in the central overlap region of the capsule; this gel persisted even after the capsule has dissolved.

Example 4

The granules of Experiment 3 were compressed into 835.4 mg caplets using a Kilian tablet press. The size of the caplet is 20 mm x 6.0 mm x 7.2 mm (length x width x thickness) with a hardness of 7-11 kp. The caplets were manually filled into size no. 00 two-piece hard gelatin capsules. The dimension of the gelatin capsule is 23.3 mm x 7.9 mm (length x internal diameter).

Dissolution was carried out according to USP 26 in 900 ml of 0.07 N HCl at 37° C, in USP apparatus II.

Time (min)	Cumulative percent drug released
15	96.6%
45	100%

The dissolution complies with the USP requirement for cefuroxime axetil of not less than 65% dissolved in 15 minutes, and not less than 75% in 45 minutes. Gel formation was not observed. The mean rupture time of the caplet-in-capsule is about three minutes.

Comparison of Example 3 and Example 4 clearly shows suppression of gel formation and thus improved dissolution when the same amount of granules is tabletted before filling into the capsule.

The bioavailability of the caplet-in-capsule formulation of Example 4 was compared to Glaxo's 500 mg film-coated tablet (Ceftin®).

COMPARISON OF PHARMACOKINETIC PARAMETERS		
Parameter	Example 4	Ceftin®
T_{max} ± S.D.	2.0 ± 0.68 h	2.0 ± 0.74 h
C_{max} ± S.D.	5.48 ± 1.53 mcg/ml	5.05 ± 1.58 mcg/ml
% reference	108%	reference
AUC $_{0\text{-}12\ h}$ ± S.D.	22.94 ± 3.32 mcg/ml-h	19.74 ± 5.17 mcg/ml-h
% reference	116%	reference

The bioavailability study was carried out in 18 volunteers under fasting conditions using a single oral dose equivalent to 500 mg of cefuroxime. The above data shows that the caplet-in-capsule formulation of Example 4 is bioequivalent to the commercial film-coated Ceftin® tablet.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

CLAIMS

We claim:

1. A pharmaceutical composition for oral administration which comprises a core tablet of cefuroxime axetil inside a capsule.

2. The composition according to Claim 1, wherein the tablet is in the shape of a capsule (caplet).

3. The composition according to Claim 2, wherein the smallest dimension of the caplet is greater or equal to 65% of the internal diameter of the capsule.

4. The composition according to Claim 3, wherein the smallest dimension of the caplet is greater or equal to 75% of the internal diameter of the capsule.

5. The composition according to Claim 4, wherein the smallest dimension of the caplet is greater or equal to 80% of the internal diameter of the capsule.

6. The composition according to Claim 1, wherein the core tablet contains more than 10% w/w of a disintegrant.

7. The composition according to Claim 6, wherein the core tablet contains more than 15% w/w of a disintegrant.

8. The composition according to Claim 7, wherein the core tablet contains more than 20% w/w of a disintegrant.

9. The composition according to Claims 6, 7, and 8, wherein the disintegrant is selected from microcrystalline cellulose, starch, croscarmellose, crospovidone, sodium starch glycolate, and combinations thereof.

10. The composition according to Claim 1, wherein the cefuroxime axetil is substantially amorphous.

11. The composition according to Claim 1, wherein the capsule is a two-piece hard gelatin capsule.

12. The composition according to Claim 1, wherein the capsule is a two-piece hydroxypropylmethylcellulose capsule.

13. The composition according to Claim 1, wherein the capsule is a two-piece capsule made of vegetable or plant-based cellulose.

14. The composition according to Claim 1, wherein the capsule is a two-piece capsule made of polysaccharide.

PHARMACEUTICAL COMPOSITIONS

ABSTRACT

A solid oral dosage composition of cefuroxime axetil comprising a tablet inside a capsule, the capsule serving to mask the bitter taste of the drug upon oral administration. This tablet-in-a-capsule format is bioequivalent to the commercial film-coated tablet.